

(19)



Europäisches Patentamt

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(11)

EP 0 726 088 A1

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:

14.08.1996 Bulletin 1996/33

(51) Int. Cl.⁶: B01F 5/10

(21) Application number: 96200138.4

(22) Date of filing: 19.01.1996

(84) Designated Contracting States:

AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL
PT SE

(30) Priority: 20.01.1995 AR 33078995

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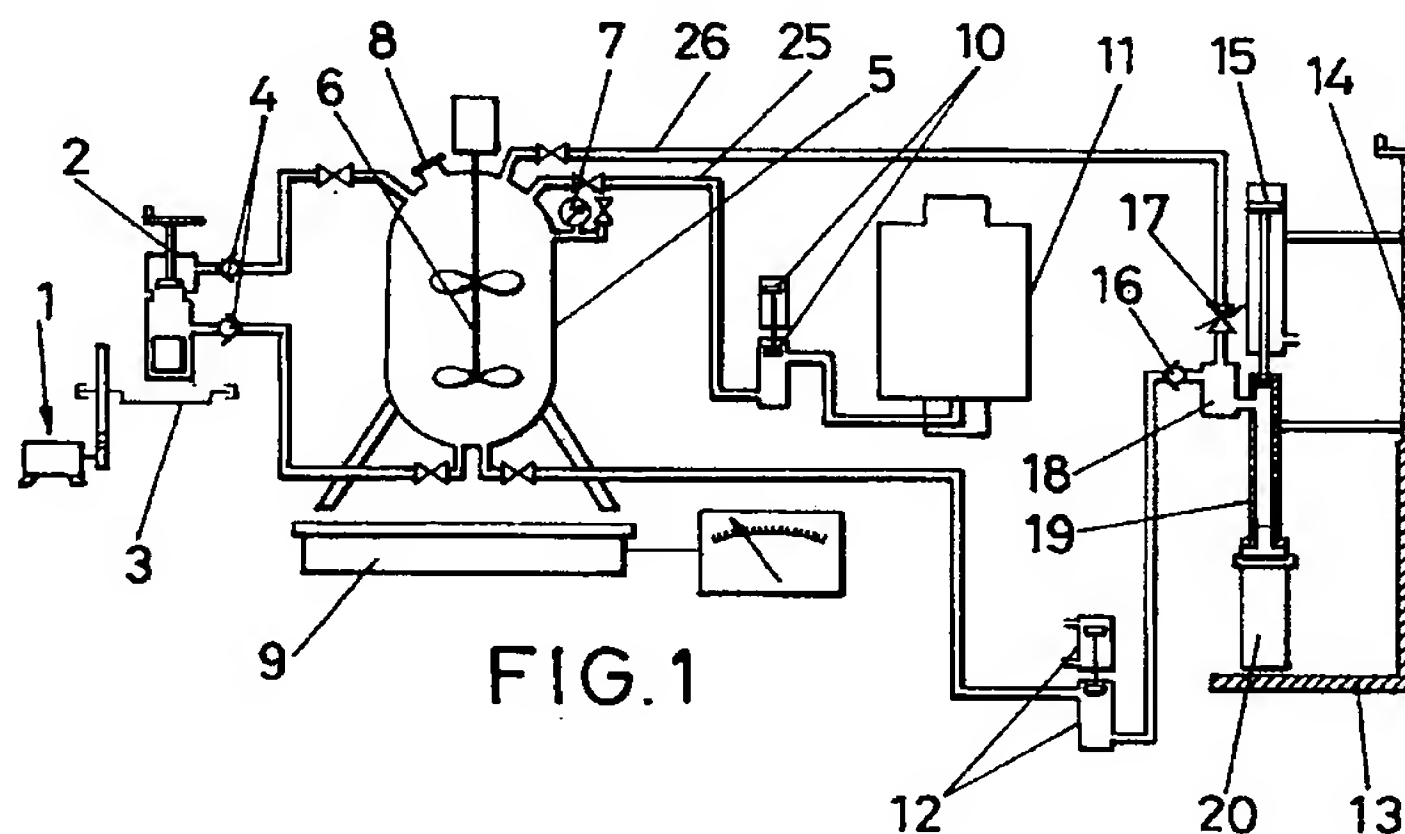
(54) Process and device for the preparation of sprayable compositions

(57) A process for manufacturing compositions dispensable as sprays, aerosols, characterized by comprising the steps of:

- maintaining in a pressurized reactor vessel (5) the active ingredient or mixture of active ingredients and additives of the composition, and a liquified propellant; said additives including dispersion stabilizing surfactant agents of said active ingredients and of the additives in the liquid phase of the propellant, under a nitrogen atmosphere which is free of oxygen;
- maintaining said mixture under constant recirculation (22,23) under high pressure conditions, forcing said mixture through plates with a plurality of micro-

apertures until obtaining a uniform dispersion of the active ingredient, or ingredients, particles; said particles being coated with a film of said stabilizing surfactants agents;

- completing the volume by adding the necessary propellant to the dispersion obtained in the previous step in order to obtain the final composition; and
- fractioning the resulting composition into dispensing containers (20) by filling the containers through the dosage valve of the container; said valve being already crimped on each container before filling.



EP 0 726 088 A1

Description

The invention relates to the manufacture of aerosols by a process by which the composition to be dispensed, without the propellant, is fractionated into the corresponding containers and the propellant is filled in through the valve already crimped on its seat. The invention also comprises a device for carrying out said process.

BACKGROUND OF THE INVENTION

Since the fifties, for different uses and purposes, an alternative manner for dispensing and dosing compositions of varied nature -both for industrial and home use- has appeared and established comprising the packing of the compositions in pressure resistant containers, generically denominated aerosols.

This denomination includes articles or devices which comprise a pressure resistant container whose contents comprise a liquid phase of a liquified compressed gas stored under pressure and temperature conditions within the container; and a product which is dissolved or dispersed in said liquid phase with the necessary additives and adjuvants.

By pressing a valve which is an integral part of a sealed assembly of the container, the contents of the container is gradually liberated in the form of fragmented tiny liquid particles, dispensed and propelled as a mist, acting as a vehicle for the components dispersed or solubilized in the liquid phase or in the propellant itself, due to the pressure differential between the external and internal atmosphere of the container.

The devices described in the prior art, grouped together under the general term aerosols (also sprays), present in practice several variations. When the product to be dispensed is a solid, the contents of the container are a dispersion of the product in the liquid phase of the propellant, with the additives and stabilizers of the dispersion, such that the propellant is part of the solvent-dispersion medium, i.e. the case of pharmaceutical aerosol (spray) inhalators.

In the pharmaceutical field, aerosols (sprays) have become very popular because of the advantages for administering active agents which have to be delivered directly to the respiratory tract (mainly bronchus and lungs) whose advantages reside mainly in the fact that the mist of ejected particles are inhaled with a minimal effort from the patient, and the inhaled product reaches directly and massively the deepest zones of the respiratory tract where it produces immediately the desired therapeutic effect. This is of tremendous importance in the case of bronchial asthma crisis or for preventing asthmatic crisis by administering programmed prophylactic dosage, avoiding the side effects common in *per os* administration.

A series of compounds generally designated as CFC and saturated hydrocarbons of low molecular weight (n-butane, isobutane, pentane, isopentane),

have been used as propellants, regardless of the purpose of the compositions or use of the same.

The CFC propellants are lower chlorofluorinated hydrocarbons which are gradually substituted by lower hydrocarbons completely fluorinated (chlorine free) due to the deleterious effect attributed to said CFC hydrocarbons on the ozone layer. The presently preferred propellants, considered as acceptable, are 134a (1,1,1,2-tetrafluoroethane) and 227-a (1,1,1,2,3,3,3-heptafluoropropane).

The conventional method for production of inhalator aerosols (sprays) comprises the steps of preparation of the product to be dispensed; filling the container with the correct amount of active ingredient, dispersion aids and propellant; and sealing the container by inserting the valve under pressure (crimping). Often the active drug is precoated with the surfactants and dried in order to facilitate its subsequent dispersion in the propellant.

This technique involves the handling of solutions, solvents and the propellant at temperatures sufficiently low and compatible with the liquid state of the propellant (cold packing).

In practice, the handling of propellant substances whose boiling point, at atmospheric pressure, ranges from -50°C to 5°C, involves the use of expensive cryogenic installations.

Another common alternative is the use of at least two propellants in which case, in which case the lower vapor pressure propellant is used as the vehicle for the components of the composition. Thus, in each container the adequate volume of the less volatile propellant is dosified, together with the necessary amounts of the components of the composition, at low temperatures, generally between about -10°C and 5°C; then the valve is crimped in place and finally the composition is completed loading the highest vapor pressure propellant through the valve.

The above mentioned techniques require a careful handling of every stage mainly because the humidity often condensates as liquid water or ice which is difficult to avoid or control even with sophisticated installations. Furthermore, even in the case of propellants freed from humidity it is impossible to avoid partial evaporation of the liquified propellant.

On the other hand, when attempting to obtain a perfect dispersion, it is necessary to pre-coat the active principles with the dispersion aids (surfactants). With the present invention, it is not necessary to pre-coat the solids with the surfactant, because the required stage through the homogenizer, incorporated to the system, forms a good coating on each solid particle delivering an homogeneous product, easy to resuspend, which is a very important feature in anti-asthma inhalators for the obtention of uniform dosages.

The inconvenients and disadvantages of conventional methods for the manufacture of aerosols can be solved by the process of the present invention in which a batch containing the active ingredient, the adjuvants and additives, and the liquid propellant in the appropri-

ate quantities are mixed together in a pressurized vessel (reactor) for subsequent filling of each individual container through the crimped valve, at room temperature.

BRIEF DESCRIPTION OF THE INVENTION

A process for the preparation of compositions which can be dispensed as sprays, comprising:

filling a container under pressure with the proper amount of the active(s) ingredient(s) of the composition; introducing in said container a fraction, by weight or volume, of the liquified propellant which is sufficient for dispensing the components and dispersion aids under permanent agitation in an oxygen free atmosphere of nitrogen;

recirculation under high pressure through multiple tiny openings in order to obtain an homogeneous dispersion and a coating of the solid particles (active drug) with the dispersion aids (surfactants).

Then, the propellant is added in small amounts maintaining active the forced recirculation scheme. The suspension is then forced into the dispensing units through the dosifying valve which has been previously crimped to each unit prior to the filling.

The present invention also comprises a device for the preparation of compositions dispensable as sprays, as later described in claim 1, characterized by comprising

a pressurized vessel comprising input means for the admission of liquid propellant,

input means for admission of the composition components; and

agitation and homogenization means for the products admitted in said container (liquid propellant and the indicated components).

BRIEF DESCRIPTION OF THE DRAWINGS

Figure N° 1 is a schematic view of the device used for manufacturing the compositions dispensable as aerosols accordingly to the present invention; and Figure N° 2 is a partial view of the device of Figure N° 1 showing in detail the pressure container associated with the homogenizing unit.

The numeral references correspond to the following elements:

1. Motor for reduction of the speed of the homogenizer
2. Circulation regulatory screw
3. Piston mechanism of the homogenizer
4. Unidirectional valves
5. Pressurized vessel where the composition to be packed is prepared
6. Agitator
7. Manometer and safety valve
8. Manually operated port

9. Scale

- 10/12. Pneumatic acting pumps
11. Propellant filling deposit
13. Table supporting the containers to be filled
14. Regulator adaptable to the containers' height
15. Pneumatic cylinder for driving the filling of the containers
16. Valve
17. Needle valve (recirculation)
18. First receptor of the filling unit
19. Piston for filling the containers
20. Container to be filled with the valve already crimped
21. Homogenizer
- 22/23. Circulation tubes of the contents of the reactor to and from the homogenizer
- 24/25'. Valves of the circulation lines
25. Charge line with propellant from the reactor
26. Liquified propellant line from the deposit
27. Composition conducting line to the container filling station

DETAILED DESCRIPTION OF THE INVENTION

In the device illustrated on Figure N° 1, the propellant is feed to the pressurized vessel or reactor (5) from the deposit of liquified propellant (11), through pipe (25) associated to a pneumatic pumping equipment (10).

The present invention is not dependent nor is associated with any specific propellant; every available propellant compatible with the active ingredient is useful and adequate with the objectives and purposes of the invention. The dosage of the propellant towards the reactor vessel is controlled by a weighing mechanism (9), which supports deposit (11). Naturally, other means to control dosage can be used.

The reactor pressurized vessel (5) is also supported on a weighing structure (9) for registering the amounts of the remaining ingredients of the composition (dispersing agents, emulsifiers and any other additives to be included in the composition) introduced through the admission part (8).

Said pressurized vessel or reactor (5) comprises means for agitation, removal, and mixing of the products introduced, including the active ingredients introduced through the manually operated port (8), or through an auxiliary feeding line (not shown). Said pressurized vessel (5) is associated to a forced recirculation circuit of the charge admitted in said vessel (5), schematically illustrated in Figure N° 2. In said circuit the mixture processed in the reactor vessel (5) is continuously drawn (line 23) from the lower part of the reactor (5) and recirculated under pressure via (22) previously passing through the homogenizer (21) until a uniform dispersion is obtained and every solid particle being coated with the dispersion aids (surfactants).

The preferred homogenizers are those of the Manton Gaulin type being a device comprising pistons which force the material of line (23), at high pressure through

plates provided with a plurality of small openings. The forced pass of the material (propellant, additives and the active agents) through the holes generates important attrition forces which determine the disintegration of the residual solid particles and the covering of each solid particle with the dispersion agents (surfactants).

Once the preparation of the composition is completed and the corresponding controls have been made the containers (20) are filled up through the already crimped valve installed in a previous operation (not shown). The completed composition is conducted through line (26) to the conventional installation or plant to fill each container.

The process and the device of the present invention allows the preparation of aerosol compositions for the pharmaceutical industry both, for internal use (aerosols for the respiratory tract or for mouth or nasal use) or for external use in administering antibiotics, anti-inflammatories, anti-histaminics, etc.

In relation with conventional techniques, the process and device of the present invention can be distinguished because:

- it does not requires cold installation or equipment;
- the possibility of water condensation in the containers is nil because the filling is accomplished in a closed circuit;
- for the same reason, the losses of propellant are avoided;
- the dosage of the compounds is more accurate because the operation is carried on a single operation, at room temperature and pressure and under an inert atmosphere (oxygen free).

The forced recirculation allows the complete coating of each of the solid particles with the dispersion aids (surfactants) thus avoiding the complex operations of the coating of the particles prior to the fabrication of the same.

In this manner, losses are avoided or substantially reduced, as well as the pre handling of the solids.

The fact that the coating is made in a sole operation, in a closed circuit and under an inert atmosphere, provides differences and operative advantages, as well as economic, as compared with conventional techniques.

Whenever necessary, depending on the propellant and the characteristics of the active ingredients, it may prove necessary to previously introduce an inert gas (such as N₂) in the reactor in order to obtain an initial internal pressure, avoid the evaporation of the propellant and provide a chemically inert medium for the active drugs.

The following example, incorporated herein merely for illustrative purposes, shows one possible embodiments of the invention:

EXAMPLE 1

The reactor vessel (5) was loaded with 2,5 Kg of propellant 134-a (tetrafluoroethane) and under continuous agitation 0,4 Kg of polioxiethylen 25-gliceriltriolate Tagat R (commercially available from Goldschmidt AG) and 0,3 Kg of Nathin 3KE (a product of Natermann Phospholipid GMBH-Köln, Germany) mixed with 0,5 Kg of absolute alcohol were added.

Maintaining agitation at room temperature, 1,760 Kg of micronized sodium chromeglycate were added. The suspension formed was recycled through the high pressure homogenizer for 30 minutes. The rest of the propellant (32,3 Kg) was added, in small fractions in a period of 2 hours maintaining constant agitation and homogenization, until a an easily resuspendable uniform suspension was obtained.

The suspension was fractioned by filling the 1/2 ounce containers, with the valve already crimped, through the 100 ml/doses valve.

Claims

1. A process for manufacturing compositions dispensable as sprays
 - aerosols- characterized by comprising the steps of:
 - maintaining in a pressurized reactor vessel the active ingredient or mixture of active ingredients and additives of the composition, and a liquified propellant; said additives including dispersion stabilizing surfactant agents of said active ingredients and of the additives in the liquid phase of the propellant, under a nitrogen atmosphere which is free of oxygen;
 - maintaining said mixture under constant recirculation under high pressure conditions, forcing said mixture through plates with a plurality of micro-apertures until obtaining a uniform dispersion of the active ingredient, or ingredients, particles; said particles being coated with a film of said stabilizing surfactants agents;
 - completing the volume by adding the necessary propellant to the dispersion obtained in the previous step in order to obtain the final composition; and
 - fractioning the resulting composition into dispensing containers by filling the containers through the dosage valve of the container; said valve being already crimped on each container before filling.
2. A process according to claim 1, characterized in that the propellant introduced in said pressurized container is a fraction, by weight or volume, of the total liquified propellant of the final composition, sufficient for dissolving-dispersing the dosified compounds in said container.

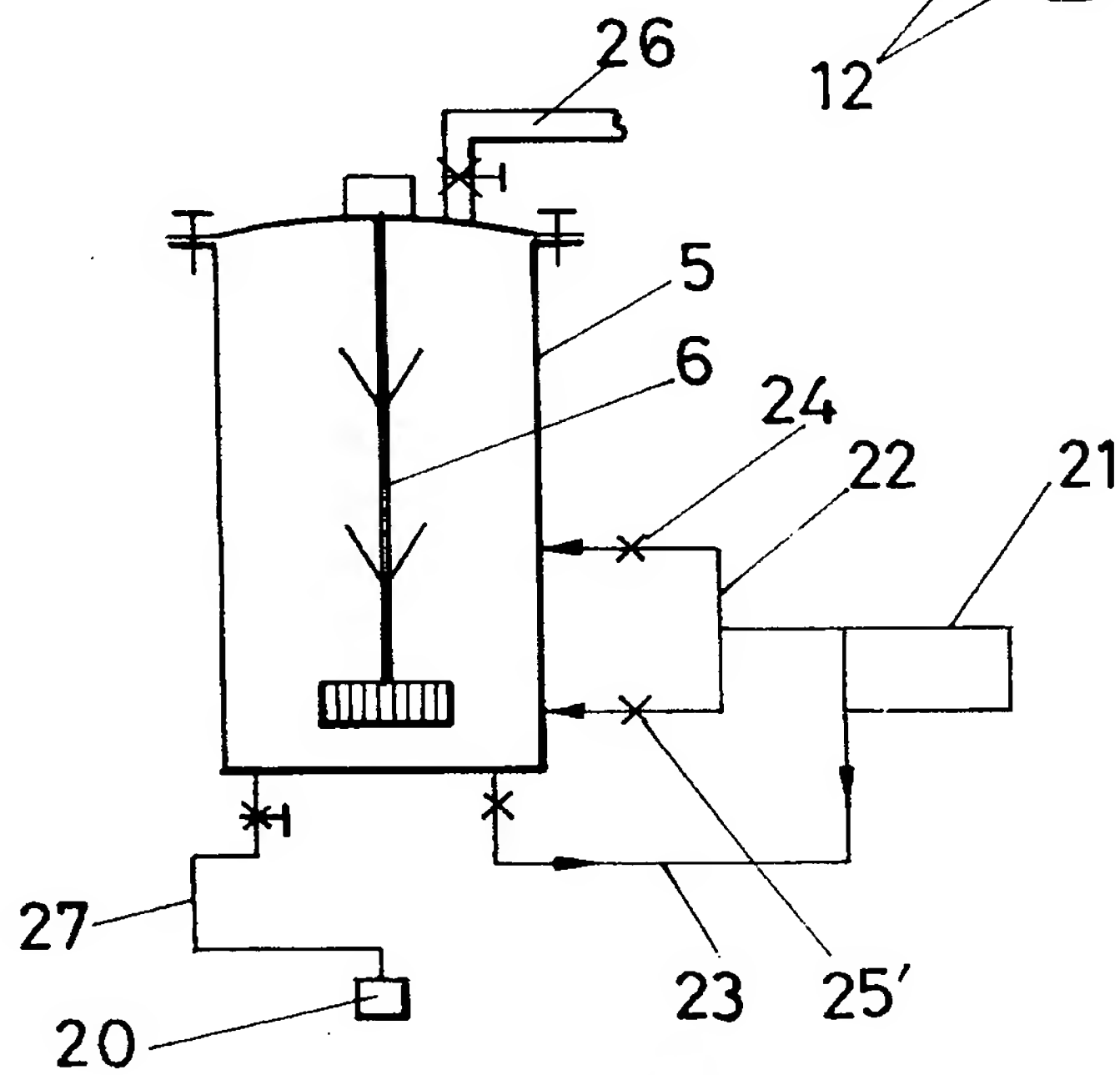
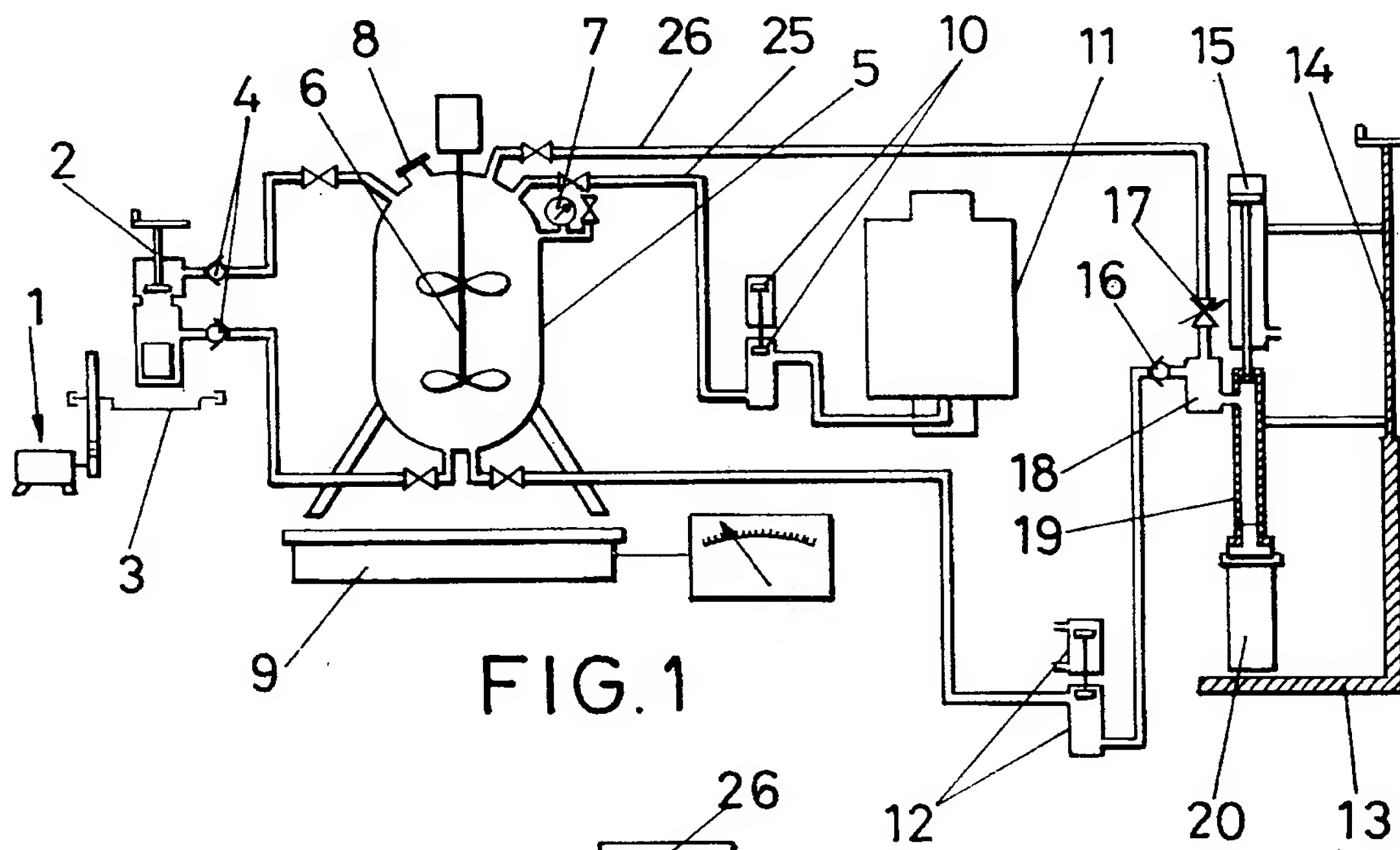
3. A process according to claim 2, characterized in that said fraction of the propellant is 1/4 of the total propellant.
4. A process according to claims 1 or 2, characterized in that said homogenizing operation is carried out by mixing and recirculating the contents of said pressurized vessel for coating the active agent particles suspended in the liquid phase of the propellant with a film of the surfactant agents which stabilize the dispersion. 5 10
5. A process according to the preceding claims, characterized in that said active ingredient is a pharmaceutical composition. 15
6. A device for the preparation of compositions dispensable as sprays in accordance with claim 1, characterized in that it comprises a pressurized vessel having means for admitting the liquified propellant; means for the admission of the composition compounds and means to provide agitation and homogenization of the products in the vessel, said products being the liquified propellant and said active ingredient and aids of the composition. 20 25
7. A device according to claim 6, characterized in that the homogenization is carried out in a closed circuit under forced recirculation between the pressurized vessel and a separate homogenizer device, both interconnected by a two way piping for the composition prepared in said pressurized vessel, said circuit including pumping means and plates with micro-apertures which are cooperating means for the homogenization and stabilization of the dispersion. 30 35

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EUROPEAN SEARCH REPORT

Application Number
EP 96 20 0138

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	FR-A-2 282 936 (HITACHI CHEMICAL CO LTD) 26 March 1976 * the whole document *	1	B01F5/10
A	WO-A-95 00321 (DOW CHEMICAL CO) 5 January 1995	1	
A	DE-A-42 37 610 (POLY ID AG STECKBORN) 19 May 1994	1	
A	PATENT ABSTRACTS OF JAPAN vol. 007, no. 252 (C-194), 9 November 1983 & JP-A-58 137435 (MITSUBISHI DENKI KK), 15 August 1983, * abstract *		
A	PATENT ABSTRACTS OF JAPAN vol. 009, no. 160 (C-289), 4 July 1985 & JP-A-60 034724 (TOYOTA JIDOSHA KK), 22 February 1985, * abstract *		
A	DE-A-23 10 027 (KUREHA CHEMICAL IND CO LTD) 4 October 1973		TECHNICAL FIELDS SEARCHED (Int.Cl.6)
A	US-A-4 518 261 (SEKIMOTO YUKIHIKO ET AL) 21 May 1985		B01F
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 4 June 1996	Examiner Gerard, O
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

EPO FORM 1503 03.92 (P04C01)

